Division of Digestive Diseases and Nutrition

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Division of Digestive Diseases and Nutrition
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3002 DEVELOPMENT OF THE GUT, LIVER AND PANCREAS (RFA DK-01-023)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-023.html

FY 2002 Action

This initiative, published on November 14, 2000, is designed to stimulate and solicit studies on gastrointestinal tract, liver and exocrine pancreas development and stem cells. Key research issues to be addressed will be: (1) how the developing endoderm gives rise to heterogeneous populations of cells in these developing and adult tissues; and (2) the molecular characterization of stem cells and their immediate descendants. Interdisciplinary projects that focus on basic developmental biology, stem cell biology and relevant clinical conditions associated with the GI tract, liver and pancreas are encouraged. In addition to hypothesis-driven R01 projects, this initiative will encourage development of new research tools through Exploratory/Developmental Grants (R21).

Background

The GI tract and related organs share common embryological origin from the endoderm. Cross-talk between endoderm and mesoderm plays an important role in specifying different components of the gut. The endoderm gives rise to gastrointestinal organs that branch from the main tube (liver, gallbladder, pancreas and cecum). Several genes have been found to be required for bud formation (e.g., *Pdx1, Hlx9, Pax4,* and *Pax6*, for pancreas and *Hex* for liver). Subsequent expansion of cellular populations in developing organs is orchestrated by a number of mesenchymal signals, such as Hlx (liver, intestinal epithelium), Pdx1 (pancreas), Cdx1 (intestinal crypts) and NKx2.3 (mid-gut epithelium). Terminal differentiation results from the interplay of both mesenchyme (genes of the Notch/Delta pathway) and epithelium (Shh). Although genes critical for patterning of the early endoderm and organogenesis have been identified, much remains to be understood about these processes. One area that needs considerable attention is the characterization of the stem cell populations in these developing organs. This requires a number of technical advances including identification of surface markers, methods for recovering these cells, clonogenic assays, and implementation of "genome anatomy projects" that will allow searchable databases of expressed genes to be developed and annotated.

Research Goals and Scope

This initiative encourages development of innovative models, approaches and reagents for characterizing the molecular properties of gastrointestinal stem cells and their differentiated descendants, as well as mesenchymal cell populations that may serve to regulate epithelial cell renewal in the developing and adult GI tract, liver and exocrine pancreas. The long-term goal of this effort is to provide a broader conceptual and experimental foundation for understanding the regulation of epithelial renewal in the normal gut and associated organs, characterizing the epithelial-mesenchymal cross-talk that underlies normal development, and for understanding the pathogenesis of disease states affecting the gut, liver, and pancreas. The initiative encourages development of new surrogate markers for identifying and classifying patient populations at risk for development of diseases affecting these organs, for following disease progression, and for characterizing therapeutic responses to existing treatment regimens. Finally, studies supported under this initiative could provide new ways for identifying therapeutic targets and strategies for disease prevention and treatment.

In addition to hypothesis-driven studies, this initiative will support exploratory/developmental efforts that seek to develop new resources for the research community. As discussed above, these resources include new methods for rapid recovery of specific cell lineages in both developing and adult GI, liver and pancreas; methods for amplifying and/or retrieving normally rare epithelial lineage progenitors from genetically defined models and the development of clonogenic assays for lineage progenitors; new and broadly applicable methods for amplifying mRNA isolated from single or small numbers of recovered cells so that gene expression profiling can be conducted; and development of systems for inducible expression of gene products in specified cell populations at specified times during development, or in adult animals.

3003 CLINICAL RESEARCH NETWORK IN NON-ALCOHOLIC STEATOHEPATITIS (RFA DK-01-025)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-025.html

FY 2002 Action

A Request for Applications (RFA) was released on February 12, 2001, to form an interlocking network of cooperative agreements to design and implement a database and clinical research network to study the etiology, contributing factors, natural history, complications, and therapy of non-alcoholic steatohepatitis (NASH). Cooperative agreements will be awarded to six clinical centers and a data coordinating center to establish a large clinical cohort of patients with NASH to be followed in a natural history study and undergo clinical investigations as to the etiology and contributing factors for development and worsening of this disease. The network is intended to provide a mechanism that will facilitate and perform clinical, epidemiological and therapeutic research in NASH.

Background

NASH is a common but poorly understood liver disease that is characterized by accumulation of fat in the liver (steatosis), accompanied by inflammation, cell injury and fibrosis (hepatitis) that closely resembles alcoholic liver disease but occurs in patients who drink little or no alcohol. NASH is most common in adults above the age of 40 who are overweight or have diabetes, insulin resistance or hyperlipidemia. However, the disease also occurs in children and in persons who are not obese or diabetic. Currently, there are no effective therapies for NASH and its natural history and prognosis are not well understood.

Research Goals and Scope

Six clinical centers and a data-coordinating center will form the NASH Clinical Research Network. The initial focus will be the development of a clinical database of patients with NASH and the development of common definitions, nomenclature and terms for the clinical diagnosis and staging of NASH. The database will be designed to address specific questions and to provide appropriate reagents or patient populations for clinical or laboratory investigation. The NASH Clinical Network is intended to provide the preliminary data and background for further investigator-initiated research and is expected to interact with basic and laboratory research investigators with interest in these diseases by providing reagents, specimens or opportunities to assess hypotheses on the pathogenesis, prevention or treatment of the disease. The Clinical Research Network will also establish pilot studies of promising therapeutic approaches and when appropriate, full scale clinical trials of therapies for NASH.

3010 INFLAMMATORY BOWEL DISEASE GENETICS RESEARCH CONSORTIUM (RFA DK-02-011)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-011.html

FY 2002 Action

On July 24, 2001, this RFA was published for an inflammatory bowel disease genetics research consortium. The study will be carried out using cooperative agreements for a single Genetic Analysis, DNA and cell line repository and Data Coordinating Center (DCC) and for multiple inflammatory bowel disease (IBD) Genetic Research Centers (GRC) to participate in the development and implementation of studies to identify genes that are associated with Crohn's disease and ulcerative colitis. The primary objective(s) of this investigation will be identification of genes or genomic regions that are associated with increased risk of IBD and with specific phenotypic manifestations, such as early age of onset, location, complications, rate of progression, response to therapy, or susceptibility to environmental risk factors.

Background

The human inflammatory bowel diseases, ulcerative colitis (UC) and Crohn's disease (CD) are relatively common chronic diseases of the gastrointestinal tract that cause significant morbidity and high utilization of health care resources. The etiology and pathogenesis of these diseases remains elusive and therapy is imperfect. A wealth of clinical and basic research information concerning IBD and related animal models has appeared in the literature in recent years. Multiple hypotheses regarding pathogenesis are currently under investigation, including, among others, possible host immune defects, differences in mucosal barrier function and mucosal repair, and interactions between the host with the GI mucosal flora. IBD may be associated with distinctly different phenotypic characteristics that may be due to differences in underlying host susceptibility and differences in environmental factors.

There is substantial evidence that genetic factors are important in IBD. Multiple lines of evidence based on twin studies, familial risk and segregation analysis have suggested that IBD is a complex, non-Mendelian genetic disorder. Between 8 and 30 percent of patients have a positive family history. Based on concordance in twin studies, a much greater role for genetic factors has been suggested for Crohn's disease than ulcerative colitis. However, the pattern of inheritance in IBD does not appear to be Mendelian. Further, the majority of patients with both diseases do not have a family history of IBD.

Multiple genes have been examined using a candidate gene approach. While HLA loci are associated with IBD in specific populations, the role of HLA genes does not appear to be dominant. Multiple groups of investigators have carried out genome wide scans using microsatellite markers in families with IBD, and a number of loci have been identified with significant, reproducible Lod scores on chromosomes 16, 12 and 1. The most widely studied locus on chromosome 16, IBD1, has been recently shown to represent mutations in the gene *Nod2*, about which relatively little is known at the present time.

There are numerous animal models of gastrointestinal inflammation, some spontaneous and some experimentally induced or related to selective gene inactivation, which have also suggested that gastrointestinal inflammatory disease is under complex genetic control and possibly intimately related to interactions of the host with the resident

microbial flora. It is expected that the identification of genetic loci that are critical in gastrointestinal inflammation in the mouse will accelerate the identification of syntenic regions in humans that may contribute to IBD, although studies of murine genetics do not fall within the scope of this solicitation.

The long-term goal of this research project is to obtain a detailed characterization of the genetic susceptibility and resistance loci for IBD, which hopefully will lead to a better understanding of disease pathogenesis, environmental modifying factors, rational design of specific pharmaceutical or biological therapies, accurate diagnostic testing for risk of IBD, and better rationale for selection of available therapies and prognosis.

Research Goals and Scope

It is the intent of this RFA to invite applications from investigators with diverse scientific interests, who wish to apply their expertise to the discovery of gene sequences associated with the development of IBD. The specific goals of this solicitation are: (1) to encourage novel approaches to identification of genes and interacting environmental factors that contribute to IBD pathogenesis through a coordinated genetic analysis and data collection center; (2) to facilitate collaborative interactions among scientists by formation of a cooperative consortium for genetic research; (3) to facilitate the recruitment of representative patients and families with well-characterized IBD for prospective studies to delineate genomic regions associated with the development and progression of disease(s); (4) to establish a resource for genetic studies of IBD by creating a DNA and cell line repository; and (5) to improve outcomes in people having or at risk for IBD through genetic research. It is anticipated that the study will take place in up to six GRCs and one DCC over a period of five years.

It is anticipated that over the five-year period, the Principal Investigators will study several cohorts of patients, families and control subjects. The individual GRCs and the DCC participating in the cooperative study should conduct mutually agreed upon protocols for characterization of study subjects and for genetic analytic strategies. The GRCs will also conduct independent analyses, and will have exclusive access to data from their study populations for a period of time, to be determined by the Steering and Planning Committee. The Steering and Planning Committee will also develop policies and procedures that permit utilization of the DNA and cell line repository by other investigators who are not members of the consortium. The design of the final research protocol for implementation, including the eligibility criteria for the final study population and the studies to be undertaken, will be effected by the Steering and Planning Committee, which will take into consideration protocols submitted and evaluated by the Scientific Review Group during the review process.

3012 SMALL CLINICAL RESEARCH GRANTS IN DIGESTIVE DISEASES AND NUTRITION (PAR-01-056)

http://grants.nih.gov/grants/guide/pa-files/PAR-01-056.html

FY 2002 Action

The Program Announcement (PA) entitled "Small Clinical Research Grants in Digestive Diseases and Nutrition" was published on February 22, 2001. This PA uses the small grant (R03) mechanism in an attempt to encourage innovative clinical and epidemiological research into new therapies or means of prevention of digestive diseases and nutritional disorders. The small grants may be used as planning grants for full-scale multi-center clinical trials or for pilot studies that could lead to full-scale multi-center clinical trials designed to provide evidence for or against changes in the current standard of care.

Background

The Division of Digestive Diseases and Nutrition began using the R03 mechanism in 1995 to support short-term clinical studies and help stimulate the translation of promising and potentially relevant new developments from the laboratory into the clinical setting. The current program announcement (PA) supersedes and expands upon the PAR-98-071, which was published in the NIH Guide on May 15, 1998. Areas of special interest in this PA include but are not limited to: inflammatory bowel disease in children and adults; motility disorders of children; celiac disease; functional bowel disease; non-ulcer dyspepsia; Barrett's esophagus; peptic ulcer disease caused by nonsteroidal anti-inflammatory agents; endoscopic management of biliary disorders; acute and chronic diverticulitis; acute and chronic pancreatitis including hereditary pancreatitis; autoimmune hepatitis; primary biliary cirrhosis; sclerosing cholangitis; Wilson's disease; biliary atresia; neonatal hepatitis; chronic hepatitis B and C; hepatotoxicity; prevention and treatment of complications of liver transplantation; living donor liver transplantation; small bowel transplantation; nutritional support of patients with intestinal failure; surgical therapy of obesity; hepatic and gastrointestinal adverse effects of medication use; binge eating disorders; anorexia nervosa and bulimia.

Research Goals and Scope

The goal of this small grants program is to provide flexibility for initiating preliminary, short-term studies, thus allowing new ideas to be investigated in a more expeditious manner without stringent requirements for preliminary data. Such support is needed to encourage experienced investigators as well as new investigators to pursue new approaches, underdeveloped topics or more risky avenues of research. If successful, these awards should lead to significant scientific advances in digestive disease and nutrition research.

3019 ADULT-TO-ADULT LIVING DONOR LIVER TRANSPLANTATION COHORT STUDY (RFA DK-02-010)
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-010.html

FY 2002 Action
This RFA was published on July 9, 2001, to invite cooperative agreement applications for clinical and coordinating centers to conduct a Living Donor Liver Transplantation (LDLT) Cohort Study among adults awaiting transplantation. The primary goal of this study will be to provide valuable information on the outcomes of LDLT. This information is needed to aid decisions made by physicians, patients and potential donors.

Adult-to-adult LDLT is a relatively new procedure increasingly used at major transplantation centers. Too few cases are performed at any one center and approaches to the patient and donor are too diverse across centers to provide reliable and generalizable information on donor and recipient outcomes from individual centers. The objective of this RFA is to establish and maintain the infrastructure required to accrue and follow sufficient numbers of patients being considered for and undergoing LDLT to provide generalizable data from adequately powered studies. This is a one-time solicitation to support a Clinical Research Consortium for seven years.

Background
Over the last 20 years liver transplantation has become the standard of care and the only cure for end stage liver disease. Its success has led to over 4,000 transplants performed yearly. But there are at least 17,000 patients on the transplantation list awaiting cadaveric liver donation. As the waiting list has expanded, waiting time has also grown. As a result, patient mortality has increased while awaiting transplantation and patients are often critically ill by the time of transplantation. Among possible remedies, living donor transplantation has become widely accepted for pediatric transplantation. Adult-to-adult LDLT is a more challenging procedure and of potentially greater risk to the donor because of the larger portion of liver that is required. Right lobe adult-to-adult LDLT is a recently developed procedure, but several hundred have already been performed in the U.S. Although still a small number relative to the several thousand adult cadaveric liver transplants performed annually, LDLT has the potential for changing the face of liver transplantation. Not only does LDLT avoid the lengthening waiting period for a cadaveric transplant, it greatly reduces the ischemic period of the transplanted organ, allows more time for evaluation of the donor, and changes the operation from an emergency into a scheduled procedure. In the special situation of hepatocellular carcinoma (HCC), early LDLT might improve survival among patients whose better liver function gives them a lower priority for cadaveric liver under current criteria. The major disadvantage of LDLT is that it is a difficult and potentially fatal operation for the donor. It also provides the recipient with a smaller portion of liver than would have been received with cadaveric transplantation.

Although many questions remain about LDLT, the pressure of the waiting list has drawn many centers to consider implementing it. As was noted at a November 2000, NIH workshop on adult LDLT, more than 20 centers in the U.S. are currently performing the procedure and at least as many are considering beginning it in the next year. As LDLT becomes more frequently used, a number of research issues need to be addressed through a prospective, multi-center, cooperative effort among centers performing the procedure.

Research Goals and Scope

The goal of this RFA is to select a Data Coordinating Center (DCC) and as many as eight Transplantation Centers (TC) to participate in planning and implementing a multi-center cohort study on adult living donor liver transplantation.

The research objectives of the LDLT Cohort Study concern factors that influence the outcomes of adult to adult LDLT. Recruited into this longitudinal cohort study would be adult patients and potential donors being considered for LDLT. Recipients and their donors would be followed for sufficient time to determine outcomes related to LDLT. These outcomes will be compared with those of appropriate comparison groups. One such comparison group might be transplant candidates who are evaluated for but do not receive LDLT. Another group might be patients not evaluated for LDLT, but who have the same diagnosis, severity of illness and other clinically significant features as patients who undergo LDLT. Regardless of the specific criteria for selecting a comparison group, the primary objective concerns comparison of morbidity and mortality of patients who receive LDLT with a group or groups of patients with similar illnesses and prognosis. A critical question to answer with this information is how do the outcomes of LDLT compare with those of cadaveric transplantation. Transplant physicians need this information on outcomes to advise patients and prospective donors. Therefore, sufficient patient and donor pairs will be recruited to determine whether recipients of LDLT have substantially different survival than non-LDLT recipients. A large number of donors and recipients from several geographically distributed institutions will be necessary to determine reliably whether outcomes are different with the two approaches.

Among other questions that could be addressed in the LDLT Cohort Study would be the following:

- What are the immediate as well as long-term risks for the donor?
- Is long-term liver function preserved for the donor?
- What is the effect of donation on the donor's quality of life?
- What are the financial and psychosocial effects on the donor?
- What is the minimal size of the donor organ?
- How does the amount of fat in a donor liver affect outcomes?
- What are the optimal operative procedures?
- Can biliary tract and other surgical complications be minimized among donors and recipients?
- Do costs differ substantially for LDLT and cadaveric transplantation?
- Do donor factors such as age, sex, and whether the donor is a first degree relative affect recipient outcomes and the need for immunosuppression?
- Can accurate markers of hepatic regeneration be identified?
- Is disease recurrence affected by LDLT?
- What is the impact of LDLT on a center's waiting time?
- What is the optimal pre-operative preparation to prevent disease recurrence, rejection and other morbidity?

3022 PATHOPHYSIOLOGICAL BASIS OF BARRETT'S ESOPHAGUS (RFA DK-02-015)

FY 2002 Action
A Request for Applications (RFA) entitled "Barrett's Esophagus, Gastroesophageal Reflux Disease and Adenocarcinoma of the Esophagus," will be released in September 2001, to stimulate studies to broadly address the problem of Barrett's esophagus (BE) and its etiology and relationship to gastroesophageal reflux disease (GERD) and its link to the rising incidence of adenocarcinoma of the esophagus. This RFA solicits RO1 grants which will examine novel approaches to molecular characterization of Barrett's esophagus, the role of environmental or genetic risk factors or the role of gastroesophageal reflux in this disease process and factors that predispose to dysplasia and malignant transformation. In addition to hypothesis driven RO1 projects, this initiative will encourage development of new research tools through the exploratory/development grants (R21). This RFA is co-sponsored by the National Cancer Institute (NCI).

Background
One of the most common gastrointestinal (GI) disorders encountered in clinical practice is reflux esophagitis. This condition is diagnosed and managed usually without difficulty. However, despite medical therapy, some patients may go on to develop complications of reflux esophagitis, i.e., esophageal ulcers, hemorrhage, stricture, or Barrett's esophagus.

Approximately two million persons in the U.S. have Barrett's esophagus. Barrett's esophagus is a condition in which the normal lining of the esophagus, stratified squamous epithelium, is replaced by columnar epithelium. It develops as a complication of chronic gastroesophageal reflux in 10 to 12 percent of patients and predisposes to the development of adenocarcinoma. Over the last two decades, the incidence of adenocarcinoma is increasing more rapidly than that of any other cancer. The reasons for this increase are unclear.

Endoscopic surveillance for early detection of adenocarcinoma is recommended for patients with Barrett's esophagus. However, there are no firm guidelines for the number of biopsies or the frequency of endoscopies in this population. Investigations targeted for understanding the transformation of esophageal lining to specialized intestinal metaplasia; for understanding the role of the cancer gene, *p53*, and other candidate genes in Barrett's esophagus; for surveillance approaches; and for the development of novel diagnostic tools will provide critical information on the progression of Barrett's esophagus to adenocarcinoma.

Research Goals and Scope
The purpose of this initiative is to solicit basic and clinical applications that will address a broad range of problems including epidemiology, mechanisms responsible for Barrett's esophagus, its progression and mechanism of transformation to dysplasia and adenocarcinoma, diagnosis, treatment and prevention.

Examples of research topics considered responsive to the RFA include, but are not limited to:

- Identification of the cells of origin of BE dysplasia, the nature of esophageal stem cells, and factors that determine differentiation of mature squamous epithelium.
- Molecular characterization of BE and dysplasia.
- Validation of animal models suitable for research on BE involving pathogenesis, prevention or treatment.
- Identification of genetic risk factors for BE, dysplasia or adenocarcinoma.
- Identification of environmental risk factors for BE, dysplasia, and adenocarcinoma.
- Identification and validation of biomarkers for BE, dysplasia, or early adenocarcinoma.
- Identification of pathophysiological steps leading from GERD to BE metaplasia: factors controlling injury and repair relevant to BE.

3024 ENVIRONMENTAL APPROACHES TO THE PREVENTION OF OBESITY (RFA DK-02-021)

FY 2002 Action
The purpose of this RFA will be to invite applications to study promising interventions that target environmental factors that contribute to inappropriate weight gain in children, adolescents and adults.

Background
Obesity is the most common nutritional disorder in the U.S., and its prevalence is increasing in both children and adults. Minority populations, particularly African American, Hispanic, and Native American women, are disproportionately affected. Although genetic factors are believed to contribute substantially to the predisposition towards obesity, environmental factors play an important role. The dramatic increase in obesity prevalence over the past two decades is believed to be a consequence of environmental factors that favor increased energy intake along with decreased energy expenditure. It has been suggested that while genetic factors may account for a significant proportion of within-population variability in body weight, environmental factors may account for most variability in body weight between populations or over time. Genetic approaches will undoubtedly provide important insights into the control of body weight, which may eventually lead to improved efforts in prevention and treatment. However, it is unlikely that addressing genetic factors alone will overcome the substantial environmental pressures for over-consumption and sedentary behavior that currently affects Americans.

Environmental factors believed to play a role in the development of obesity include those that increase energy intake, such as advertisements for and low price of high-energy density foods, consumption of larger portion sizes, greater frequency of restaurant meals, and the use of more fast-foods and convenience foods. For infants, bottle-feeding may also increase energy intake relative to breastfeeding. Numerous environmental factors also lead to decreased energy expenditure. Work is more likely to be sedentary than in the past, with near universal use of automated equipment and electronic communications. At home, wireless phones, remote controls, and various labor saving devices for household chores also decrease physical activity. More time is spent using the computer, watching television, and playing video games, particularly among children and adolescents. At the same time, the number of schools requiring daily physical education has declined. Suburban communities often lack sidewalks, and lack of neighborhood resources make it difficult to walk even short distances to stores and recreation. Many individuals report difficulties going out to exercise because their neighborhoods are perceived as unsafe. In addition, children in day care or before and after school care often lack facilities to engage in, or adequate supervision for, active play.

Prevention of obesity is frequently attempted through educational approaches aimed at improving knowledge and motivation, with consequent presumed impact on individual lifestyle choices. Such approaches have been largely ineffective at preventing weight gain. Other prevention strategies have focused on changing individual behaviors related to dieting and physical activity, but have limited applicability to large populations. In contrast, environmental and policy approaches attempt to modify the environment in which such choices are made, rather than relying on individual will. Policy approaches

are environmental interventions that involve establishing social, economic, or legal structures within a formal governmental or non-governmental organization.

Environmental changes that reinforce factors supporting healthy lifestyles and reduce barriers to healthy lifestyles may also serve to diminish health disparities, as barriers may be more prevalent in disadvantaged and ethnic minority communities. Environmental approaches that modify the environment to promote healthful eating, increase physical activity, and decrease sedentary behaviors, offer the potential for safe and effective programs for obesity prevention that could be widely disseminated. The NIDDK will invite applications to study promising interventions that would target environmental factors that contribute to inappropriate weight gain in children, adolescents and adults. Investigators should collaborate with organizations/institutions such as schools, supermarkets, restaurants, religious organizations, recreation facilities, industry, governmental or community groups, worksites, and so forth, to develop approaches that, if successful, could potentially be translated into larger-scale interventions.

The need for an obesity prevention initiative has been recognized by a number of NIH advisory groups. In 1994, the National Task Force on Prevention and Treatment of Obesity developed a long-range plan focused on prevention of obesity and recently reaffirmed obesity prevention as a priority area for clinical research. The recently issued NHLBI/NIDDK Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults include a discussion of the importance of preventing obesity and suggestions for strategies to be attempted. This review includes recommendations for research on obesity prevention. The February 1998, NHLBI Report of the Task Force on Behavioral Research in Cardiovascular, Lung and Blood Health and Disease also has recommended development of obesity prevention research efforts. In December 2000, the Surgeon General held a listening session in an effort to develop a national action plan to combat overweight and obesity. The session identified obesity prevention as a critical target, and suggested that efforts focus on environmental factors, including the family and community, schools, work sites, the health care delivery system, and the media.

Research Goals and Scope

This RFA responds to the need for systematic studies of environmental approaches to the prevention of obesity. Although many environmental factors have been cited as contributing to obesity, there have been few controlled studies showing that changes in these environmental factors will prevent weight gain. The sponsoring organizations will encourage submission of grants for innovative studies with a goal of modifying the individual, family, group, or community environment such that inappropriate weight gain is prevented by improvements in diet, increases in physical activity, and/or decreases in sedentary behaviors. For purposes of this RFA, prevention of obesity includes the primary prevention of overweight and/or obesity, the prevention of additional weight gain or increase in body fat in those already overweight and/or obese, and prevention of weight regain following weight loss. However, studies of weight management programs or use of medications or dietary supplements to prevent weight gain are not appropriate. Applications should address: the content of the intervention (e.g., relative focus on aspects of diet, physical activity, sedentary behaviors, combinations of these, or other factors), the setting of the intervention (e.g., in health care settings, community groups, recreation facilities, home, school), and the method of intervention delivery (e.g.,

individual, family, group, community). Applications targeting groups or populations at high risk for the development of obesity will be encouraged.

3025 INNOVATIVE AND EXPLORATORY RESEARCH IN DIGESTIVE DISEASES AND NUTRITION (PA-01-129)
http://grants.nih.gov/grants/guide/pa-files/PA-01-129.html

FY 2002 Action
The aim of this program announcement, released on August 20, 2001, is to stimulate the application of highly novel approaches to important areas of digestive disease and nutrition research. This program will be supported through the exploratory/developmental grant (R21) mechanism. This provides short-duration support for preliminary studies of a highly speculative or innovative nature which are expected to yield, within the two-year time frame, sufficient information upon which to base a well-planned and rigorously defined series of further investigations. This mechanism is primarily aimed at attracting and supporting new investigators in these research fields.

Background
Recent advances in basic scientific disciplines including genetics, stem cell research, and cell and molecular biology, the availability of massive databases such as that generated by the Human Genome Project and novel experimental and computational technologies for biomedical research present unprecedented opportunities for the discovery of the pathophysiological bases of important digestive and liver diseases. High impact research involves feasibility studies in which the technological, methodological or theoretical approach to a problem lacks an historical precedent or sufficient preliminary data, but whose successful outcome would have a major effect on a scientific area.

Research Goals and Scope
The goals of this program are to stimulate the application of highly novel research approaches and to attract new investigators to the field of digestive, liver and nutritional disorders. The program will provide short-duration support for preliminary studies of a highly speculative nature which are expected to yield, within the two-year time frame, sufficient information upon which to base a well-planned and rigorous series of further investigations.

3026 LIVER AND PANCREATIC DISEASE IN HIV INFECTION (PA-01-117)
http://grants.nih.gov/grants/guide/pa-files/PA-01-117.html

FY 2002 Action
This Program Announcement (PA) was published on July 17, 2001, and invites clinical and basic research applications that focus on the pathogenesis and therapeutics of the liver and pancreatic disease associated with co-infections that occur in patients with HIV infection or the metabolic complications associated with treatment of HIV infection. The co-infections targeted by this PA specifically include hepatitis B (HBV) and hepatitis C (HCV), which are frequent causes of end-stage liver disease, a leading cause of death in HIV infected patients. Metabolic complications, involving the liver and pancreas, associated with the treatment of HIV infection include: hepatic drug toxicity, hepatic lipid metabolism, nonalcoholic steatohepatitis (NASH) and pancreatitis, which are all important causes of morbidity in patients with HIV infection. The proposed studies should advance our understanding of the pathogenesis of liver and pancreatic disease in patients with HIV and/or metabolic complications of therapy. These advances should lead to enhanced medical management of individuals infected with HIV.

Background
The current initiative specifically targets hepatic and pancreatic comorbidities in the context of HIV infection, and metabolic complications of antiretroviral treatment in support of basic and clinical research that addresses the significant emerging clinical issues of disease progression in patients with HIV infection.

Highly-active antiretroviral therapy (HAART) has slowed the progression of HIV disease and decreased the rate of HIV-associated mortality. In the context of enhanced longevity for HIV patients, other comorbidities, such as chronic liver disease and pancreatitis, can assume greater importance in the medical management of patients. Based on shared routes of transmission, HBV and HCV infection are common in HIV-infected patients. HIV infection has a significant effect on the natural history of HBV infection with co-infected individuals more likely experience severe liver disease. Individuals treated with lamivudine as part of their antiretroviral treatment more frequently fail treatment, resulting in the emergence of drug resistant strains of HBV. Several studies have also documented that HIV modifies the natural history of chronic HCV infection leading to an accelerated course of progression to end-stage liver disease and death. The accelerated course to end-stage liver disease has been suggested to be reduced from the two to four decade time-frame for HCV mono-infection to as little as five to six years in HCV/HIV co-infected patients. The result of the common occurrence of hepatitis and HIV co-infection and accelerated disease progression is the report that end-stage liver disease is now the leading cause of death in hospitalized HIV-infected patients.

The etiology and pathogenesis of enhanced progression to end-stage liver disease in HIV co-infected patients is unknown. Recent data have shown that hepatitis co-infection results in enhanced liver disease in individuals infected with HIV through enhanced severity of fibrosis, a higher frequency of cirrhosis and end-stage liver disease as well as increased deaths due to liver disease. The role of HCV quasispecies, the effects of immune deficiency on the course of hepatitis C, hepatotoxicity due to antiretroviral treatment, chronic HBV infection, immune restoration and HBV infection, and development of nonalcoholic steatohepatitis (NASH) as a result of lipodystrophy have all

been hypothesized to play a role in the enhanced liver disease seen in co-infected individuals. Additional research is needed to identify the mechanism(s) of pathogenesis and to identify therapeutic targets for treatment.

Research Goals and Scope

This initiative will support basic and clinical research in HIV co-infection and metabolic disease related to antiretroviral treatment. Areas of interest include but are not limited to:

- The elucidation of biological mechanism(s) that promote enhanced progression of liver disease in HIV-infected patients.
- A further elucidation of drug-induced hepatotoxicity associated with anti-retroviral treatment regimens.
- The identification of therapeutic targets and/or novel therapies for the treatment of liver disease in HIV-infected patients.
- The elucidation of synergy between HIV and HCV, resulting in enhanced liver disease.
- The enhanced knowledge of antiviral treatment failures of HBV/HIV co-infection and the emergence of HBV drug-resistant strains.
- The identification of underlying liver disease, such as NASH, in combination with HIV infection and antiretroviral treatment, that progresses to end-stage liver disease.
- Therapeutics development for the enhanced medical management of patients with HBV/HIV or HCV/HIV co-infection or metabolic abnormalities due to antiretroviral treatment.
- Altered hepatic lipid metabolism due to antiretroviral treatment.
- HIV-associated pancreatitis and risk factors, including hypertriglyceridemia, obesity and gallstones.
- The impact of liver transplantation on disease progression in select patients with co-infection with Hepatitis B or Hepatitis C.

3027 BILIARY ATRESIA CLINICAL RESEARCH CONSORTIUM (RFA DK-02-008)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-008.html

FY 2002 Action

A Request for Applications (RFA) was released on June 28, 2001, to form an interlocking network of cooperative agreements to engage in a collaborative clinical research consortium to establish a database of clinical information and serum and tissue samples from children with biliary atresia and idiopathic neonatal hepatitis. The Biliary Atresia Clinical Research Consortium will facilitate and perform clinical, epidemiological and therapeutic research in biliary atresia and idiopathic neonatal hepatitis, two important and rare pediatric liver diseases.

Background

Jaundice and hyperbilirubinemia that extends beyond the immediate newborn period are usually due to either biliary atresia or idiopathic neonatal hepatitis. Biliary atresia, although a rare disease, is the most common reason for liver transplantation in children. Its etiology, however, remains elusive and its optimal management is still unsettled. Idiopathic neonatal hepatitis can resemble biliary atresia clinically but is usually a self-limited illness that does not lead to cirrhosis or the need for liver transplantation. The cause of neonatal hepatitis is also unknown; however, it appears to be non-infectious in etiology. There are too few new cases of biliary atresia and neonatal hepatitis seen each year at a single pediatric liver disease center to allow for intensive analyses of risk factors or for critical assessment of different means of diagnosis and treatment. Thus, a collaborative consortium of pediatric hepatology and transplant centers is needed to gather sufficient data and adequate numbers of serum and tissue samples in a prospective manner to facilitate research and generate hypotheses on the pathogenesis and optimal treatment modalities of biliary atresia and neonatal hepatitis.

Research Goals and Scope

A Biliary Atresia Clinical Research Consortium of eight to ten pediatric clinical research centers and a data coordinating center with expertise in biliary atresia and neonatal hepatitis will be established to accelerate advances in the understanding, diagnosis and clinical management of these rare, pediatric liver diseases. The initial focus will be the development of a clinical database of patients with biliary atresia and neonatal hepatitis with an emphasis on developing common definitions, nomenclature and terms for the clinical diagnosis of biliary atresia and neonatal hepatitis. Histological criteria for the diagnosis, standard diagnostic algorithms, clinical definitions, means of assessing symptoms and quality of life, standardized forms and questionnaires, and agreed upon essential information for the diagnosis and characterization of a patient cohort will be defined. The database will be designed to address specific questions and to provide appropriate reagents or patient populations for clinical or laboratory investigation. The Biliary Atresia Clinical Research Consortium will also provide the preliminary data and background for further investigator-initiated research and will be expected to interact with basic and laboratory research investigators with interest in these diseases by providing reagents, serum or DNA specimens and other resources to help assess hypotheses on the pathogenesis, prevention or treatment of the disease.

3029 ADDITIONAL DIGESTIVE DISEASES CENTER (RFA DK-01-027)
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-027.html

FY 2002 Action
The Silvio O. Conte Digestive Diseases Research Core Centers (DDRCC) program will be expanded to a total of fifteen P30 centers in FY 2002. This follows the addition of a new Center in FY 2000 to Washington University and another new Center in FY 2001 to Baylor College of Medicine. The DDRCC program had been supporting a total of twelve centers since 1987 until this recent three-year period of growth. Both the number and quality of applications for this program warrants the expansion.

DIVISION OF DIGESTIVE DISEASES AND NUTRITION
Conferences and Workshops

ERCP: State of the Science
(Co-sponsored by the NIH Office of Medical Applications of Research)
This international conference will be modeled after consensus conferences and will bring together expert speakers in different aspects of ERCP to present evidence based reviews on specific topics regarding this commonly used diagnostic and therapeutic endoscopic procedure. In addition, a panel of experts in different aspects of medicine, gastroenterology and evidence based review will summarize the state of the science regarding the use of this technology following the expert presentations.

NIH Consensus Conference—Management of Hepatitis C Update
(Co-sponsored by the NIH Office of Medical Applications of Research)
September 2002
Since the last NIH Consensus Conference on management of hepatitis C there have been a number of important advances in the field and further progress in and refinement of approaches to therapy. The conference will use the NIH Consensus Conference format of having presentations on specific topics by authorities followed by review and a consensus statement by a panel of outstanding generalists of diverse background. A major evidence based review of the literature will be included in the overall summary of the meeting.

Clinical Endpoints for Clinical Research in Inflammatory Bowel Diseases
Clinical research in IBD is hampered by difficulties in defining specific phenotypes of disease, assessing activity of disease and changes in disease in response to therapeutic interventions. The goal of the workshop will be to bring together experts from NIH, FDA, the IBD research community, the pharmaceutical industry and clinical trial design to formulate improved approaches to defining clinical endpoints for clinical trials in IBD.